SEQUENCE LISTING

<110> Yacoby-Zeevi, Oron Peretz, Tuvia Miron, Daphna Shlomi, Yinon Pecker, Iris Ayal-Hershkovitz, Maty Feinstein, Elena Van Gelder, Joel M. Vlodavsky, Israel Friedmann, Yael <130> 26128

HEPARANASE ACTIVITY NEUTRALIZING ANTI- HEPARANASE MONOCLONAL ANTIBODY AND OTHER ANTI-HEPARANASE ANTIBODIES

<160> 16

<170> PatentIn version 3.3

<210> 386 <211>

<212>` PRT

<213> Homo sapiens

<220>

misc feature

45 kDa subunit of mature processed heparanase dimer

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Tyr Thr Phe Ala Asn Cys Ser Gly Leu Asp Leu Ile Phe Gly Leu Asn 20 25 30

Ala Leu Leu Arg Thr Ala Asp Leu Gln Trp Asn Ser Ser Asn Ala Gln

Leu Leu Leu Asp Tyr Cys Ser Ser Lys Gly Tyr Asn Ile Ser Trp Glu 50 60

Leu Gly Asn Glu Pro Asn Ser Phe Leu Lys Lys Ala Asp Ile Phe Ile 65 70 75 80

Asn Gly Ser Gln Leu Gly Glu Asp Phe Ile Gln Leu His Lys Leu Leu 85 90 95

Arg Lys Ser Thr Phe Lys Asn Ala Lys Leu Tyr Gly Pro Asp Val Gly 100 105 110

Gln Pro Arg Arg Lys Thr Ala Lys Met Leu Lys Ser Phe Leu Lys Ala 115 120 125

Gly Gly Glu Val Ile Asp Ser Val Thr Trp His His Tyr Tyr Leu Asn 130 135 140

Gly Arg Thr Ala Thr Arg Glu Asp Phe Leu Asn Pro Asp Val Leu Asp 145 150 155 160

Ile Phe Ile Ser Ser Val Gln Lys Val Phe Gln Val Val Glu Ser Thr 165 170 175

Arg Pro Gly Lys Lys Val Trp Leu Gly Glu Thr Ser Ser Ala Tyr Gly 180 185 190

Gly Gly Ala Pro Leu Leu Ser Asp Thr Phe Ala Ala Gly Phe Met Trp 195 200 205

Arg Gln Val Phe Phe Gly Ala Gly Asn Tyr His Leu Val Asp Glu Asn 225 230 235 240

Phe Asp Pro Leu Pro Asp Tyr Trp Leu Ser Leu Leu Phe Lys Lys Leu 245 250 255

Val Gly Thr Lys Val Leu Met Ala Ser Val Gln Gly Ser Lys Arg Arg 260 265 270

Lys Leu Arg Val Tyr Leu His Cys Thr Asn Thr Asp Asn Pro Arg Tyr 275 280 285

Lys Glu Gly Asp Leu Thr Leu Tyr Ala Ile Asn Leu His Asn Val Thr $290 \hspace{1.5cm} 295 \hspace{1.5cm} 300 \hspace{1.5cm}$

Lys Tyr Leu Arg Leu Pro Tyr Pro Phe Ser Asn Lys Gln Val Asp Lys 305 310315315

Tyr Leu Leu Arg Pro Leu Gly Pro His Gly Leu Leu Ser Lys Ser Val 325 330 335

Gln Leu Asn Gly Leu Thr Leu Lys Met Val Asp Asp Gln Thr Leu Pro $340 \hspace{1.5cm} 345 \hspace{1.5cm} 345 \hspace{1.5cm} 350 \hspace{1.5cm}$

Pro Leu Met Glu Lys Pro Leu Arg Pro Gly Ser Ser Leu Gly Leu Pro 355 360 365

Ala Phe Ser Tyr Ser Phe Phe Val Ile Arg Asn Ala Lys Val Ala Ala 370 375 380

Cys Ile 385

210> 2

<211> 535

<212> PRT

<213> Mus musculus

<400> 2

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Leu Glu Phe Tyr Thr Lys Arg Pro Leu Arg Ser Val Ser Pro Ser Phe 35 40 45

Leu Ser Ile Thr Ile Asp Ala Ser Leu Ala Thr Asp Pro Arg Phe Leu 50 60

Thr Phe Leu Gly Ser Pro Arg Leu Arg Ala Leu Ala Arg Gly Leu Ser 65 70 75 80

Pro Ala Tyr Leu Arg Phe Gly Gly Thr Lys Thr Asp Phe Leu Ile Phe $85 \hspace{1cm} 90 \hspace{1cm} 95$

Gln Val Asn His Asp Ile Cys Arg Ser Glu Pro Val Ser Ala Ala Val 115 120125

Leu Arg Lys Leu Gln Val Glu Trp Pro Phe Gln Glu Leu Leu Leu 130 135 140

Arg Glu Gln Tyr Gln Lys Glu Phe Lys Asn Ser Thr Tyr Ser Arg Ser 145 150155160

Ser Val Asp Met Leu Tyr Ser Phe Ala Lys Cys Ser Gly Leu Asp Leu 165 170 175

Ile Phe Gly Leu Asn Ala Leu Leu Arg Thr Pro Asp Leu Arg Trp Asn 180 \$180\$

Ser Ser Asn Ala Gln Leu Leu Leu Asp Tyr Cys Ser Ser Lys Gly Tyr 195 200 205

Asn Ile Ser Trp Glu Leu Gly Asn Glu Pro Asn Ser Phe Trp Lys Lys 210 215 220

Ala His Ile Leu Ile Asp Gly Leu Gln Leu Gly Glu Asp Phe Val Glu 225 230 235 240

Leu His Lys Leu Gln Arg Ser Ala Phe Gln Asn Ala Lys Leu Tyr $245 \hspace{1.5cm} 250 \hspace{1.5cm} 255 \hspace{1.5cm}$

Gly Pro Asp Ile Gly Gln Pro Arg Gly Lys Thr Val Lys Leu Leu Arg 260 265 270

Ser Phe Leu Lys Ala Gly Gly Glu Val Ile Asp Ser Leu Thr Trp His 275 280 285

His Tyr Tyr Leu Asn Gly Arg Ile Ala Thr Lys Glu Asp Phe Leu Ser 290 295 300

Ser Asp Ala Leu Asp Thr Phe Ile Leu Ser Val Gln Lys Ile Leu Lys 305 310 315 320

Val Thr Lys Glu Ile Thr Pro Gly Lys Lys Val Trp Leu Gly Glu Thr 325 330 335 Ser Ser Ala Tyr Gly Gly Gly Ala Pro Leu Leu Ser Asn Thr Phe Ala 340 345 350

Ala Gly Phe Met Trp Leu Asp Lys Leu Gly Leu Ser Ala Gln Met Gly 355 360 365

 Leu Val Asp Glu Asn
 Phe Glu Pro Leu Pro Asp Tyr
 Trp Leu Ser Leu 385
 Leu 400

Leu Phe Lys Lys Leu Val Gly Pro Arg Val Leu Leu Ser Arg Val Lys 405 410 415

Gly Pro Asp Arg Ser Lys Leu Arg Val Tyr Leu His Cys Thr Asn Val 420 425

Tyr His Pro Arg Tyr Gln Glu Gly Asp Leu Thr Leu Tyr Val Leu Asn 435 440 445

Leu His Asn Val Thr Lys His Leu Lys Val Pro Pro Pro Leu Phe Arg 450 455 460

Lys Pro Val Asp Thr Tyr Leu Leu Lys Pro Ser Gly Pro Asp Gly Leu 465 470 480

Leu Ser Lys Ser Val Gln Leu Asn Gly Gln Ile Leu Lys Met Val Asp 485 490 495

Glu Gln Thr Leu Pro Ala Leu Thr Glu Lys Pro Leu Pro Ala Gly Ser 500 505 510

Ala Leu Ser Leu Pro Ala Phe Ser Tyr Gly Phe Phe Val Ile Arg Asn 515 520 525

Ala Lys Ile Ala Ala Cys Ile 530 535

<210> 3

<211> 536

<213> Rattus norvegicus

<400> 3

Met Leu Arg Pro Leu Leu Leu Trp Leu Trp Gly Arg Leu Arg Ala 1 $$ 5 $$ 10 $$ 15

Leu Thr Gln Gly Thr Pro Ala Gly Thr Ala Pro Thr Lys Asp Val Val $20 \\ 25 \\ 30$

Asp Leu Glu Phe Tyr Thr Lys Arg Leu Phe Gln Ser Val Ser Pro Ser 35 40 45

Phe Leu Ser Ile Thr Ile Asp Ala Ser Leu Ala Thr Asp Pro Arg Phe 50 55 60

Leu Thr Phe Leu Gly Ser Pro Arg Leu Arg Ala Leu Ala Arg Gly Leu 65 70 75 80

Ser Pro Ala Tyr Leu Arg Phe Gly Gly Thr Lys Thr Asp Phe Leu Ile 85 90 95

Phe Asp Pro Asn Lys Glu Pro Thr Ser Glu Glu Arg Ser Tyr Trp Gln 100 105 110

Ser Gln Asp Asn Asn Asp Ile Cys Gly Ser Glu Arg Val Ser Ala Asp 115 120 125

Val Leu Arg Lys Leu Gln Met Glu Trp Pro Phe Gln Glu Leu Leu Leu 130 135 140

Leu Arg Glu Gln Tyr Gln Arg Glu Phe Lys Asn Ser Thr Tyr Ser Arg 145 150 155 160

Ser Ser Val Asp Met Leu Tyr Ser Phe Ala Lys Cys Ser Arg Leu Asp 165 170 175

Leu Ile Phe Gly Leu Asn Ala Leu Leu Arg Thr Pro Asp Leu Arg Trp 180 185 190

Asn Ser Ser Asn Ala Gln Leu Leu Leu Asn Tyr Cys Ser Ser Lys Gly 195 200 205

Tyr Asn Ile Ser Trp Glu Leu Gly Asn Glu Pro Asn Ser Phe Trp Lys 210 215 220

Lys Ala Gln Ile Ser Ile Asp Gly Leu Gln Leu Gly Glu Asp Phe Val 225 230 240

Glu Leu His Lys Leu Leu Gln Lys Ser Ala Phe Gln Asn Ala Lys Leu 245 250 255

Tyr Gly Pro Asp Ile Gly Gln Pro Arg Gly Lys Thr Val Lys Leu Leu 260 265 270

Arg Ser Phe Leu Lys Ala Gly Gly Glu Val Ile Asp Ser Leu Thr Trp 275 280 285

His His Tyr Tyr Leu Asn Gly Arg Val Ala Thr Lys Glu Asp Phe Leu 290 295 300

Ser Ser Asp Val Leu Asp Thr Phe Ile Leu Ser Val Gln Lys Ile Leu 305 310 315 320

Lys Val Thr Lys Glu Met Thr Pro Gly Lys Lys Val Trp Leu Gly Glu 325 330 335

Thr Ser Ser Ala Tyr Gly Gly Gly Ala Pro Leu Leu Ser Asn Thr Phe $340 \hspace{1cm} 345 \hspace{1cm} 350$

Ala Ala Gly Phe Met Trp Leu Asp Lys Leu Gly Leu Ser Ala Gln Leu

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Gly Ile Glu Val Val Met Arg Gln Val Phe Phe Gly Ala Gly Asn Tyr 370 375 380

His Leu Val Asp Glu Asn Phe Glu Pro Leu Pro Asp Tyr Trp Leu Ser 385 390 395 400

Leu Leu Phe Lys Lys Leu Val Gly Pro Lys Val Leu Met Ser Arg Val 405 415

Lys Gly Pro Asp Arg Ser Lys Leu Arg Val Tyr Leu His Cys Thr Asn 420 425 430

Val Tyr His Pro Arg Tyr Arg Glu Gly Asp Leu Thr Leu Tyr Val Leu 435. 440 445

Asn Leu His Asn Val Thr Lys His Leu Lys Leu Pro Pro Met Phe 450 455 460

Ser Arg Pro Val Asp Lys Tyr Leu Leu Lys Pro Phe Gly Ser Asp Gly 465 . 470 475 480

Leu Leu Ser Lys Ser Val Gln Leu Asn Gly Gln Thr Leu Lys Met Val 485 490

Asp Glu Gln Thr Leu Pro Ala Leu Thr Glu Lys Pro Leu Pro Ala Gly 500 505 510

Ser Ser Leu Ser Val Pro Ala Phe Ser Tyr Gly Phe Phe Val Ile Arg 515 520 525

Asn Ala Lys Ile Ala Ala Cys Ile 530 535

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<211> 543 <212> PRT

<213> Homo sapiens

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Leu Leu Gly Pro Leu Gly Pro Leu Ser Pro Gly Ala Leu Pro Arg Pro 20 25 30

Ala Gln Ala Gln Asp Val Val Asp Leu Asp Phe Phe Thr Gln Glu Pro 35 40 45

Leu His Leu Val Ser Pro Ser Phe Leu Ser Val Thr Ile Asp Ala Asn 50 55 60

Leu Ala Thr Asp Pro Arg Phe Leu Ile Leu Leu Gly Ser Pro Lys Leu 65 70 75 80

Arg Thr Leu Ala Arg Gly Leu Ser Pro Ala Tyr Leu Arg Phe Gly Gly

Thr Lys Thr Asp Phe Leu Ile Phe Asp Pro Lys Lys Glu Ser Thr Phe

Glu Glu Arg Ser Tyr Trp Gln Ser Gln Val Asn Gln Asp Ile Cys Lys 115 120 125

Tyr Gly Ser Ile Pro Pro Asp Val Glu Glu Lys Leu Arg Leu Glu Trp 130 135 140

Pro Tyr Gln Glu Gln Leu Leu Leu Arg Glu His Tyr Gln Lys Lys Phe 145 \$150\$ L55 \$160

Lys Asn Ser Thr Tyr Ser Arg Ser Ser Val Asp Val Leu Tyr Thr Phe 165 170 175

Ala Asn Cys Ser Gly Leu Asp Leu Ile Phe Gly Leu Asn Ala Leu Leu 180 185 190

Arg Thr Ala Asp Leu Gln Trp Asn Ser Ser Asn Ala Gln Leu Leu 195 200 205

Asp Tyr Cys Ser Ser Lys Gly Tyr Asn Ile Ser Trp Glu Leu Gly Asn 210 215 220

Glu Pro Asn Ser Phe Leu Lys Lys Ala Asp Ile Phe Ile Asn Gly Ser 225 230 240

Gln Leu Gly Glu Asp Phe Ile Gln Leu His Lys Leu Leu Arg Lys Ser 245 250 255

Thr Phe Lys Asn Ala Lys Leu Tyr Gly Pro Asp Val Gly Gln Pro Arg 260 265 270

Arg Lys Thr Ala Lys Met Leu Lys Ser Phe Leu Lys Ala Gly Glu 275 280 285

Val Ile Asp Ser Val Thr Trp His His Tyr Tyr Leu Asn Gly Arg Thr 290 295 300

Ala Thr Arg Glu Asp Phe Leu Asn Pro Asp Val Leu Asp Ile Phe Ile 305 310 315 320

Ser Ser Val Gln Lys Val Phe Gln Val Val Glu Ser Thr Arg Pro Gly 325 330 335

Lys Lys Val Trp Leu Gly Glu Thr Ser Ser Ala Tyr Gly Gly Gly Ala $340 \hspace{1cm} 345 \hspace{1cm} 350$

Pro Leu Leu Ser Asp Thr Phe Ala Ala Gly Phe Met Trp Leu Asp Lys 355 360 365

Leu Gly Leu Ser Ala Arg Met Gly Ile Glu Val Val Met Arg Gln Val 370 375 380

Phe Phe Gly Ala Gly Asn Tyr His Leu Val Asp Glu Asn Phe Asp Pro 385 390 395 400

Leu Pro Asp Tyr Trp Leu Ser Leu Leu Phe Lys Lys Leu Val Gly Thr $405 \hspace{1cm} 415 \hspace{1cm}$

Lys Val Leu Met Ala Ser Val Gln Gly Ser Lys Arg Arg Lys Leu Arg 420 425 430

Val Tyr Leu His Cys Thr Asn Thr Asp Asn Pro Arg Tyr Lys Glu Gly 435 440 445

Asp Leu Thr Leu Tyr Ala Ile Asn Leu His Asn Val Thr Lys Tyr Leu 450 455 460

Arg Leu Pro Tyr Pro Phe Ser Asn Lys Gln Val Asp Lys Tyr Leu Leu 465 470 475 480

Arg Pro Leu Gly Pro His Gly Leu Leu Ser Lys Ser Val Gln Leu Asn 485 490 495

Gly Leu Thr Leu Lys Met Val Asp Asp Gln Thr Leu Pro Pro Leu Met 500 505 510

Glu Lys Pro Leu Arg Pro Gly Ser Ser Leu Gly Leu Pro Ala Phe Ser 515 520 525

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<211> 523

<212> PRT

<213> Gallus gallus

<400> 5

Met Leu Val Leu Leu Leu Leu Val Leu Leu Leu Ala Val Pro Pro Arg 1 5 10 15

Arg Thr Ala Glu Leu Gln Leu Gly Leu Arg Glu Pro Ile Gly Ala Val 20 25 30

Ser Pro Ala Phe Leu Ser Leu Thr Leu Asp Ala Ser Leu Ala Arg Asp $35 \hspace{1cm} 40 \hspace{1cm} 45$

Pro Arg Phe Val Ala Leu Leu Arg His Pro Lys Leu His Thr Leu Ala 50 60

Ser Gly Leu Ser Pro Gly Phe Leu Arg Phe Gly Gly Thr Ser Thr Asp 65 70 75 80

Phe Leu Ile Phe Asn Pro Asn Lys Asp Ser Thr Trp Glu Glu Lys Val 85 90 95

Leu Ser Glu Phe Gln Ala Lys Asp Val Cys Glu Ala Trp Pro Ser Phe $100 \hspace{1.5cm} 105 \hspace{1.5cm} 105 \hspace{1.5cm} 110 \hspace{1.5cm}$

Ala Val Val Pro Lys Leu Leu Leu Thr Gln Trp Pro Leu Gln Glu Lys 115 120 125

Leu Leu Leu Ala Glu His Ser Trp Lys Lys His Lys Asn Thr Thr Ile 130 135 140

Thr Arg Ser Thr Leu Asp Ile Leu His Thr Phe Ala Ser Ser Ser Gly 145 150 155

Phe Arg Leu Val Phe Gly Leu Asn Ala Leu Leu Arg Arg Ala Gly Leu 165 170 175

Gln Trp Asp Ser Ser Asn Ala Lys Gln Leu Leu Gly Tyr Cys Ala Gln 180 185 190

Arg Lys Lys Ser Gly Ile Cys Ile Asp Gly Phe Gln Leu Gly Arg Asp 210 215 220

Phe Val His Leu Arg Gln Leu Leu Ser Gln His Pro Leu Tyr Arg His 225 235 240

Ala Glu Leu Tyr Gly Leu Asp Val Gly Gln Pro Arg Lys His Thr Gln 245 250 255

Val Thr Trp His His Tyr Tyr Val Asn Gly Arg Ser Ala Thr Arg Glu $275 \cdot 280$ 285

Asp Phe Leu Ser Pro Glu Val Leu Asp Ser Phe Ala Thr Ala Ile His 290 295300

Asp Val Leu Gly Ile Val Glu Ala Thr Val Pro Gly Lys Lys Val Trp 305 310 315 320

Leu Gly Glu Thr Gly Ser Ala Tyr Gly Gly Gly Ala Pro Gln Leu Ser 325 330 . 335

Asn Thr Tyr Val Ala Gly Phe Met Trp Leu Asp Lys Leu Gly Leu Ala 340 345 350

Ala Arg Arg Gly Ile Asp Val Val Met Arg Gln Val Ser Phe Gly Ala 355 \$360\$

Gly Ser Tyr His Leu Val Asp Ala Gly Phe Lys Pro Leu Pro Asp Tyr 370 375 380

Trp Leu Ser Leu Leu Tyr Lys Arg Leu Val Gly Thr Arg Val Leu Gln 385 390 400

Ala Ser Val Glu Gln Ala Asp Ala Arg Arg Pro Arg Val Tyr Leu His 405 410 415

10 Cys Thr Asn Pro Arg His Pro Lys Tyr Arg Glu Gly Asp Val Thr Leu 420 425 430Phe Ala Leu Asn Leu Ser Asn Val Thr Gln Ser Leu Gln Leu Pro Lys 435 440 445Gln Leu Trp Ser Lys Ser Val Asp Gln Tyr Leu Leu Leu Pro His Gly 450 455 460 Lys Asp Ser Ile Leu Ser Arg Glu Val Gln Leu Asn Gly Arg Leu Leu 465 470 480 Gln Met Val Asp Asp Glu Thr Leu Pro Ala Leu His Glu Met Ala Leu 485 490 495 Ala Pro Gly Ser Thr Leu Gly Leu Pro Ala Phe Ser Tyr Gly Phe Tyr 500 505 510Val Ile Arg Asn Ala Lys Ala Ile Ala Cys Ile 515 520 <210> <211> 10 <212> PRT <213> Artificial sequence <220> <223> Functional peptide epitope of heparanase <400> 6 Cys Thr Asn Thr Asp Asn Pro Arg Tyr Lys 1 5 10<210> <211> 19 <212> PRT <213> Artificial sequence <223> Functional peptide epitope of heparanase Pro Ala Tyr Leu Arg Phe Gly Gly Thr Lys Thr Asp Phe Leu Ile Phe 1 $$ 5 $$ 10 $$ 15 Asp Pro Lys <210> <211> 15 <212> PRT <213> Artificial sequence <220> <223> Functional peptide epitope of heparanase

Ser Trp Glu Leu Gly Asn Glu Pro Asn Ser Phe Leu Lys Lys Ala 1 5 10

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      PRT
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      Artificial sequence
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<223> Functional peptide epitope of heparanase
Thr Trp His His Tyr Tyr Leu Asn Gly Arg Thr Ala Thr Arg
<210>
<211> 74
<212> PRT
<213> Homo sapiens
<220>
<221>
      misc feature
<223> 8 kDa subunit of mature processed heparanase dimer
Gln Asp Val Val Asp Leu Asp Phe Phe Thr Gln Glu Pro Leu His Leu
Val Ser Pro Ser Phe Leu Ser Val Thr Ile Asp Ala Asn Leu Ala Thr 20 25 30
Asp Pro Arg Phe Leu Ile Leu Leu Gly Ser Pro Lys Leu Arg Thr Leu 35 40 45
Ala Arg Gly Leu Ser Pro Ala Tyr Leu Arg Phe Gly Gly Thr Lys Thr
Asp Phe Leu Ile Phe Asp Pro Lys Lys Glu 65
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       8
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<213> Artificial sequence
<223> HS-binding protein consensus sequence
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       (1)...(1)
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<220>
<221> misc_feature
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<222> (2)..(4)
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       Basic amino acid residue
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<221>
       misc_feature
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       (5) . . (6)
<223> Xaa can be any naturally occurring amino acid
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       (7) \cdot (7)
<223> Basic amino acid residue
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<222> (8)..(8)
<223> Xaa can be any naturally occurring amino acid
<400> 12
Xaa Xaa Xaa Xaa Xaa Xaa Xaa
      . 5
<210> 13
<211> 6
<212> PRT
<213> Artificial sequence
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<223> HS-binding protein consensus sequence
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<221> misc_feature
<222> (1)..(1)
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<221> misc_feature
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       (2)...(3)
<223> Basic amino acid residue
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       (4) . . (4)
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       (5)..(5)
<223> Basic amino acid residue
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<222> (6)..(6)
<223> Xaa can be any naturally occurring amino acid
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Xaa Xaa Xaa Xaa Xaa
1 5
<210> 14
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<212> PRT
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Gln Lys Lys Phe Lys Asn
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Pro Arg Arg Lys Thr Ala Lys Met
1 5

<210> 16
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